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(54) O/W EMULSION COMPOSITIONS

(57) The present invention relates to an O/W emulsion composition characterized by comprising fluorometholone or clobetasone butyrate, a phospholipid, an oil, a nonionic water-soluble cellulose derivative, and water.

The O/W composition of the present invention has advantages that fluorometholone or clobetasone butyrate contained therein is highly soluble in body fluids and that the solubility of fluorometholone or clobetasone butyrate and the concentration thereof contained in the composition can be kept stable. Thus, this composition is usable for the treatment of various inflammatory diseases by the generalized or local administration thereof. The present invention provides a drug which shows an anti-inflammatory activity equal or higher than that of commercially available eye drops comprising a suspension of such an active ingredient even when it is applied in a smaller dose than that of commercially available one and further provides a drug having excellent storability, which reduces apprehension of systemic side effects of fluorometholone or clobetasone butyrate when it is applied to the eyes.

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Description

Technical Field

[0001] The present invention relates to an O/W emulsion composition in which fluorometholone or clobetasone butyrate is highly soluble in body fluids such as blood and lachrymal fluid and having excellent property of keeping the solubility and concentration of fluorometholone or clobetasone butyrate contained in the composition.

Background Art

[0002] Fluorometholone and clobetasone butyrate are synthetic adrenocortical hormones having a strong anti-inflammatory activity. Fluorometholone is effective in the treatment of the inflammatory diseases of outer ocular area and anterior segment of the eye, and clobetasone butyrate is effective in the treatment of the inflammatory diseases of eyes and also those of the skin. It is expected that these drugs are also effective in the treatment of the local and generalized inflammatory diseases other than those described above. However, because these drugs are hardly soluble in water, it is impossible to dispense these drugs in the form of ordinary aqueous preparations such as eye drops and parenteral injections. Therefore, in the ophthalmic field, fluorometholone and clobetasone butyrate have been each used in the form of an aqueous suspension which is prepared by finely pulverizing the crystals thereof and dispersing and suspending a suitable amount of the fine crystals in an aqueous liquid for eye drops. However, because these drugs are hardly soluble in water, the degree of dissolution of these drugs in the form of crystalline particles, contained in the aqueous suspension, into the lachrymal fluid is low and, accordingly, the bioavailability is extremely low.

[0003] It is known that the bioavailability of a hardly soluble drug generally depends on the solubility of the drug in water. For example, when such a hardly soluble drug is administered in the form of an oral solid preparation, the rate of release of the drug from the preparation thereof and dissolution of the drug are the rate-controlling step for the absorption of the drug (see "*Iyakuhin no Bioavailability to Seibutsugaku-teki Dotosei Shiken*" written by Hiroyasu Ogata and Masayoshi Samejima and published by Yakugyo Jiho, inc.). In addition, when such a hardly soluble drug in the form of its suspension is applied to the eyes, transition of the drug into the eye tissue depends on the dissolution rate of the drug from the crystalline particles diluted with the lachrymal fluid [J. Pharm. Sci., 64 (6), 931-936 (1975)]. Namely, the bioavailability can be improved if the concentration of the administered, hardly soluble drug in the body fluids could be increased.

[0004] WO 97/05882 discloses that an O/W emulsion comprising fluorometholone or clobetasone butyrate as a drug, a phospholipid, a liquid paraffin and water improves the solubility of the drug in the lachrymal fluid to improve transfer of the drug into the eye tissue. However, this publication is silent on the influence of the additives on the nature of the composition to improve the solubility of fluorometholone or clobetasone butyrate in the lachrymal fluid, and also on the additives used for improving the solubility. This publication is also silent on the stability of the dissolution concentration of these drugs in the lachrymal fluid and of the concentration of these drugs in the composition during the storage. The inventors examined the storability of the emulsion preparations to find that both fluorometholone and clobetasone butyrate were crystallized during the storage and the ability of the composition to improve the solubility of these drugs in the lachrymal fluid were lowered.

[0005] As for the techniques of improving the stability of such a kind of emulsion, various emulsions comprising a water-soluble polymer were disclosed [see WO 93/15736, WO 96/40051, Japanese Patent Unexamined Published Application (hereinafter referred to as "J. P. KOKAI") No. Sho 53-121920, J. Soc. Cosmet. Chem., 37, 329-350 (1986), J. SCCJ, 27 (3), 206-215 (1993), and Int. J. Pharm., 140 (1), 97-109 (1996)]. However, these prior techniques are silent on the solubility of the drug in the body fluids and also on the improvement in the stability of the concentration of the drug contained in the composition (hereinafter referred to as "drug concentration"). J. P. KOKAI No. Hei 5-186333 discloses that an ophthalmic O/W emulsion composition comprising a drug, an oil, a phospholipid and an amphoteric surfactant is capable of keeping the average particle diameter and the drug concentration thereof during the storage.

Disclosure of the Invention

[0006] The present invention has been developed for the purposes of improving the solubility of the conventional, hardly water-soluble drug in the body fluid and the stability of the improved solubility of the drugs in the body fluids. The object of the present invention is to provide a novel composition containing fluorometholone or clobetasone butyrate highly soluble in body fluids such as blood and lachrymal fluid and having excellent property of keeping the solubility of these drugs into body fluids and concentration of fluorometholone or clobetasone butyrate contained in the composition. After intensive investigations made for the purpose of attaining the above-described object, the inventors have found that an O/W emulsion composition containing fluorometholone or clobetasone butyrate, a phospholipid, an oil, a nonionic water-soluble cellulose derivative and water shows a high solubility of fluorometholone or clobetasone butyrate

in the body fluids and such a high solubility thereof and the concentration of fluorometholone or clobetasone butyrate contained in the composition can be kept stable during the storage. The inventors have further found that when at least one member of the group consisting of chelating agents, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof is incorporated into the emulsion composition, the solubility of fluorometholone or clobetasone butyrate in the body fluids and the concentration of fluorometholone or clobetasone butyrate contained in the composition can be kept stable for a far longer period of time. The present invention has been completed on the basis of these findings.

[0007] Namely, the present invention provides an O/W emulsion composition containing fluorometholone or clobetasone butyrate, a phospholipid, an oil, a non-ionic water-soluble cellulose derivative and water and, if necessary, at least one member of the group consisting of chelating agents, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof. The present invention is characterized in that the solubility of fluorometholone and clobetasone butyrate in the body fluids is improved by incorporating the nonionic water-soluble cellulose derivative as an indispensable component. Other characteristic features of the present invention are that the solubility of fluorometholone and clobetasone butyrate in the body fluids is high and that the concentration of fluorometholone and clobetasone butyrate in the composition can be kept stable during the storage. By suitably changing the proportion of the constituents and amounts thereof, the O/W emulsion composition having a particularly high solubility of fluorometholone or clobetasone butyrate in the body fluids can be obtained, and the solubility and the concentration of fluorometholone or clobetasone butyrate contained in the composition can be kept stable for a longer period of time in the present invention. The O/W emulsion composition containing fluorometholone or clobetasone butyrate can be given to the patients by the systemic administration method or topical administration method in a suitable preparation form such as liquids for internal use, injections, ear drops, nasal drops, eye drops, aerosols or inhalations depending on the need. The O/W emulsion composition is usable for the treatment of diseases such as chronic hypoadrenocorticism, acute chronic hypoadrenocorticism, chronic articular rheumatism, ankylosing spondylitis, lupus erythematodes, systemic angitis, polymyositis, nephrosis and nephrotic syndrome, congestive heart failure, bronchial asthma, asthmatic bronchitis, allergy and intoxication caused by drugs and other chemical substances, severe infectious diseases, hemolytic anemia, leukemia, aplastic anemia, localized enteritis, tumorous colitis, fulminant hepatitis, chronic hepatitis, hepatic cirrhosis, sarcoidosis, diffuse interstitial pneumonia, post-invasion pulmonary edema, tuberculous meningitis, tuberculous pleurisy, tuberculous peritonitis, tuberculous pericarditis, encephalomyelitis, peripheral neuritis, spinal arachnoiditis, malignant lymphoma, adrenalectomy, organ and tissue transplantation, snake poison, insect poison, acute eczema, chronic eczema, contact dermatitis, autosensitization dermatitis, atopic dermatitis, neurodermatitis, dermatitis seborrhoica, hives, psoriasis and analogous diseases, anaphylactoid purpura, mucocutaneos ocular syndrome, Raynaud's disease, pemphigus group, herpes zoster, allergic angitis and analogous diseases, inflammatory diseases of intaocular, optic nerve, orbit and ocular muscle, inflammatory diseases of outer ocular area and anterior segment of the eye (when the application of eye drops is unsuitable or insufficient in the symptomatic therapy), acute and chronic otitis media, vasomotor rhinitis, allergic rhinitis, pollenosis, progressive gangrenous rhinitis, pharyngeal catarrh and pharyngeal enema, pharyngeal polyp and nodule, esophagitis and esophageal dilation operation (aftercare), otorhinolaryngologic operation (aftercare), intractable stomatitis and glossitis, acute and chronic (recurrent) sialadenitis, anaphylactic shock, retinochoroiditis, retinal vasculitis, optic neuritis, orbital inflammatory pseudotumor, orbital apex syndrome, opthalmoplegia, inflammatory diseases of outer ocular area and anterior segment of the eye such as blepharitis, conjunctivitis, keratitis, scleritis, episcleritis, iritis, iridocycitis, uveitis and postoperative inflammations.

Description of the Preferred Embodiments:

[0008] The detailed description will be made below on the present invention.

[0009] The nonionic, water-soluble cellulose derivatives contained in the O/W emulsion composition (hereinafter referred to as "emulsion") of the present invention are not particularly limited. They include, for example, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose and hydroxyethylmethylcellulose. The degree of substitution and viscosity grade of the nonionic, water-soluble cellulose derivative are not particularly limited. The nonionic, water-soluble cellulose derivatives having any degree of substitution and any viscosity grade are usable in the present invention. At least one of the nonionic, water-soluble cellulose derivatives is incorporated into the emulsion of the present invention.

[0010] Among those nonionic, water-soluble cellulose derivatives, methylcellulose and hydroxypropylmethylcellulose are preferred because when either of them is used, a high concentration of fluorometholone (hereinafter referred to as "FLM") or clobetasone butyrate (hereinafter referred to as "CB") dissolved in the body fluids can be obtained, and the dissolution concentration thereof and also the concentration of FLM or CB contained in the composition (hereinafter referred to as "FLM concentration" or "CB concentration") can be kept stable for a longer period of time. Methylcellulose is the most preferred.

[0011] These nonionic, water-soluble cellulose derivatives are easily available on the market under the trade names

of Metolose (registered trademark) SM-15, Metolose SM-25, Metolose SM-100, Metolose SM-400, Metolose SM-1500, Metolose SM-4000 and Metolose SM-8000 (methylcellulose; products of Shin-Etsu Chemical Co., Ltd.); TC-5E, TC-5MW, TC-5R, TC-5S, Metolose (registered trademark) 60SH-50 and Metolose 60SH-4000 (Hydxoxypropylmethylcellulose 2910; Shin-Etsu Chemical Co., Ltd.); Metolose (registered trademark) 65SH-50, Metolose 65SH-400, Metolose 65SH-1500 and Metolose 65SH-4000 (Hydroxypropylmethylcellulose 2906; Shin-Etsu Chemical Co., Ltd.); SB-4, Metolose (registered trademark) 90SH-100, Metolose 90SH-400, Metolose 90SH-4000 and Metolose 90SH-30000F (Hydroxypropylmethylcellulose 2208; Shin-Etsu Chemical Co., Ltd.); FUJICHEMI HEC CF-H (hydroxyethylcellulose; Fuji Chemical Co., Ltd.); Tylose (registered trademark) H300G4PHA (hydroxyethylcellulose; Clariant (Japan) K.K.); Shin-Etsu HPC (hydroxypropylcellulose; Shin-Etsu Chemical Co., Ltd.); and Tylopur (registered trademark) MH300G4 (hydroxyethylmethylcellulose; Clariant (Japan) K.K.).

[0012] The amount of the nonionic, water-soluble cellulose derivative used is usually 0.0005 to 5 w/v%, preferably 0.001 to 1 w/v%, more preferably 0.005 to 0.5 w/v%, and most preferably 0.025 to 0.5 w/v%. When the amount of the nonionic, water-soluble cellulose derivative used is 0.0005 w/v% or higher, the stability of the dissolution concentration of FLM or CB in the body fluids and the concentration of FLM or CB in the composition during the storage can be kept high. When the amount of the nonionic, water-soluble cellulose derivative used is 5 w/v% or less, the obtained emulsion has a low viscosity to make the administration thereof easy and a comfortable feeling is recognized when the emulsion is used as eye drops. It is preferable to use the amount of the nonionic, water-soluble cellulose derivative in the range of 0.025 to 0.5 w/v% since the obtained emulsion shows particularly high stability of the dissolution concentration of FLM or CB in the body fluids and the concentration of FLM or CB.

[0013] The chelating agents, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof used in the present invention are not particularly limited. They include, for example, ethylenediamine-tetraacetic acid (EDTA), citric acid, thiomalic acid, L-glutamic acid, succinic acid, malonic acid, maleic acid, dl-malic acid, adipic acid, tartaric acid, D-tartaric acid, fumaric acid, L-aspartic acid, glycyrrhizic acid, hydroxyethylethylenediaminetriacetic acid, diethylenetriamine-pentaacetic acid and pharmaceutically acceptable salts of them, and L-cystine. At least one of the group consisting of these chelating agents, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof is incorporated into the emulsion of the present invention. Among these chelating agents, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof, EDTA, citric acid and pharmaceutically acceptable salts thereof, which are widely used for eye drops, are preferred.

[0014] The pharmaceutically acceptable salts of EDTA usable in the present invention are, for example, sodium edetate (disodium edetate), tetrasodium edetate (tetrasodium edetate dihydrate), tetrasodium edetate tetrahydrate and calcium disodium edetate. Examples of the pharmaceutically acceptable salts of citric acid usable in the present invention are sodium citrate (trisodium citrate), disodium citrate (dibasic sodium citrate), trisodium citrate, sodium dihydrogen citrate, calcium citrate, dipotassium hydrogen citrate, potassium dihydrogen citrate and tripotassium citrate monohydrate.

[0015] The chelating agent, polycarboxylic acid compound and pharmaceutically acceptable salt thereof are used each in an amount of usually 0.0001 to 0.2 w/v%, preferably 0.0004 to 0.18 w/v%, more preferably 0.0005 to 0.18 w/v%, and most preferably 0.0025 to 0.05 w/v%. When the amount of the chelating agent, polycarboxylic add compound and pharmaceutically acceptable salt thereof is 0.000 1 w/v% or higher, the dissolution concentration of each of FILM and CB in the body fluids and the stability of the concentration of FLM and CB during the storage are high. When the amount of the chelating agent, polycarboxylic acid compound and pharmaceutically acceptable salt thereof is 0.2 w/v% or less, the stability of the emulsion is high. The amount of the chelating agent, polycarboxylic acid compound and pharmaceutically acceptable salt thereof in the range of 0.0025 to 0.05 w/v% is preferable. Because the obtained emulsion shows a particularly high stability of the dissolution concentration of FLM or CB in the body fluids and of the concentration of FLM or CB during the storage. In addition, this emulsion is free from the color change and oil drop formation (or oil separation) during the storage.

[0016] The drug in the emulsion of the present invention is FLM or CB, and the concentration thereof is usually 0.001 to 0.5 w/v%, preferably 0.005 to 0.1 w/v%. When the concentration of FLM or CB is 0.001 w/v% or higher, the dissolution concentration thereof in the body fluids is high. When the concentration of FLM or CB is 0.5 w/v% or less, this drug is not easily crystallized during the storage. The concentration of FLM or CB in the range of 0.005 to 0.1 w/v% is preferred because the obtained emulsion shows a particularly high stability of the dissolution concentration of FLM or CB in the body fluids and of the concentration of FLM or CB during the storage.

[0017] The phospholipids used in the present invention are not particularly limited. They are, for example, yolk lecithin, soybean lecithin, as well as lyso-forms and hydrogenated products thereof, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, dicetyl phosphate, sphingomyelin; synthetic phospholipids such as dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine and distearoyl phosphatidylcholine; and mixtures of these phospholipids. At least one phospholipid selected from among the above-described group of the phospholipids is incorporated into the emulsion of the present invention.

[0018] These phospholipids are easily available on the market under the trade names of, for example, Coatsome

(registered trademark) NC-10S (high purity yolk lecithin; a product of NOF Corporation), purified egg yolk lecithin (Asahi Chemical Industry Co., Ltd.), Egg yolk lecithin PL-100H, ditto PL-100E, ditto PL-100LE and ditto PC-98N (Q. P. Corporation), Powdery egg yolk lecithin (hydrogenated and purified yolk lecithin) R-27, ditto R-20 and ditto R-5 (Asahi Chemical Industry Co., Ltd.), PCS (soybean phosphatidylcholine; Nippon Fine Chemical Co., Ltd.), PCSH (hydrogenated soybean phosphatidylcholine; Nippon Fine Chemical Co., Ltd.), Coatsome (registered trademark) NC-21 (hydrogenated soybean lecithin; NOF Corporation), Egg yolk lecithin LPL-20 (Q. P. Corporation), Coatsome (registered trademark) MC-6060 (L-α-dipalmitoyl phosphatidylcholine; NOF Corporation), Coatsome (registered trademark) MA-6060 (L-α-dipalmitoyl phosphatidic acid; NOF Corporation), Coatsome (registered trademark) MGLS-6060 (Na salt of L-α-dipalmitoyl phosphatidyl-DL-glycerol; NOF Corporation), Coatsome (registered trademark) MGLA-6060 (NH_4 salt of L-α-dipalmitoyl phosphatidyl-DL-glycerol; NOF Corporation), Sphingolipid CB-1 (a sphingolipid; Q. P. Corporation), etc.

[0019] When FLM is incorporated as the drug into the emulsion of the present invention, the amount of the phospholipid used is usually 10 to 150 parts by weight, preferably 20 to 100 parts by weight and more preferably 40 to 100 parts by weight, per one part by weight of FLM. In case the phospholipid is contained in the emulsion in an amount of at least 10 parts by weight per one part by weight of FLM, FLM is not easily crystallized during the storage. Also, by using the phospholipid in an amount of not larger than 150 parts by weight per one part by weight of FLM, the dissolution concentration of FLM in the body fluids is high. It is preferred to use phospholipid in an amount in the range of 40 to 100 parts by weight per one part by weight of FLM because the obtained emulsion has a particularly high stability of the dissolution concentration of FLM in the body fluids and of the concentration of FLM in the composition during the storage.

[0020] When CB is incorporated as the drug into the emulsion of the present invention, the amount of the phospholipid used is usually 5 to 100 parts by weight, preferably 10 to 80 parts by, per one part by weight of CB. By using the phospholipid in an amount of at least 5 parts by weight per one part by weight of CB, CB is not easily crystallized during the storage. Also, by using the phospholipid in an amount of not larger than 100 parts by weight per one part by weight of CB, the dissolution concentration of CB in the body fluids is high. It is preferable to use phospholipid in an amount in the range of 10 to 80 parts by weight per one part by weight of CB because the obtained emulsion has a particularly high stability of the dissolution concentration of CB in the body fluids and of the concentration of CB in the composition during the storage.

[0021] An emulsifying adjuvant may be added to the phospholipids. Examples of the emulsifying adjuvant include sterols such as cholesterol; aliphatic amines such as stearylamine; saturated and unsaturated fatty acids such as stearic acid, palmitic acid, myristic acid, linoleic acid and oleic acid; and pharmaceutically acceptable salts (such as sodium salts and potassium salts) of them. Although the amount of the emulsifying adjuvant is not particularly limited, usually it is not larger than 0.2 part by weight per one part by weight of the phospholipid.

[0022] The oil used in the present invention is not particularly limited. The oils are, for example, vegetable oils such as soybean oil, sesame oil, corn oil, peanut oil, olive oil, safflower oil, jojoba oil, cotton seed oil and rapeseed oil; oils derived from animal oils and fats such as squalane; mono-, di- and triglycerides of fatty acids having 6 to 18 carbon atoms (such as caproic acid, stearic acid, palmitic acid, myristic acid and linoleic acid) such as glycerol tricaprylate and tricaprylin and mixtures of them; mineral oils such as liquid paraffin and light liquid paraffin; silicone oil; and fatty acid esters. The viscosity and specific gravity of these oils are not particularly limited. The oils having any viscosity and specific gravity are usable in the present invention. At least one of the oils of the above-described group is incorporated into the emulsion of the present invention.

[0023] These oils are easily available on the market under the trade names of Purified soybean oil (Showa Sangyo Co., Ltd.), Purified olive oil (Showa Sangyo Co., Ltd.), NIKKOL Safflower Oil (Nikko Chemicals Co., Ltd.), NIKKOL Jojoba Oil E (Nikko Chemicals Co., Ltd.), NIKKOL Triester F-810 (medium-length chain fatty acid triglycerides; Nikko Chemicals Co., Ltd.), Panasate 810 (medium-length chain fatty acid triglycerides; NOF Corporation), NIKKOL Trifat P-52 (hydrogenated palm oil fatty acid triglycerides; Nikko Chemicals Co., Ltd.), NIKKOL MGS-A (glycerol monostearate; Nikko Chemicals Co., Ltd.), NIKKOL IPM-EX (isopropyl myristate; Nikko Chemicals Co., Ltd.), NIKKOL IPP (isopropyl palmitate; Nikko Chemicals Co., Ltd.), Toray • Dow • Corning • Silicone SH200C-100cs (Toray Dow Corning Silicone Corp., Light Liquid Paraffin No. 70-S, Liquid Paraffin No 150-S, Liquid Paraffin No. 260-S and Liquid Paraffin No. 350-S (Sanko Chemical Industry Co. Ltd.).

[0024] Among these oils, the liquid paraffin is preferred because the color change of the emulsion during the storage is only slight when it is used.

[0025] When FLM is incorporated as the active ingredient, the amount of the oil used is usually 0.5 to 20 parts by weight, preferably 1 to 10 parts by weight, per one part by weight of the phospholipid, and the oil concentration in the emulsion is preferably not higher than 25 w/v%. When the amount of the oil used together with FLM is in the range of 0.5 to 20 parts by weight per one part by weight of the phospholipid, the stability of the emulsion during the storage is high. When the amount of the oil used together with FLM is at least 0.5 % by weight per one part by weight of the phospholipid, the color change during the storage is only slight. The oil concentration in the emulsion is preferably 25 w/v% or below because an emulsion having a low viscosity can be obtained, which can be easily administered, and when the

emulsion is used as eye drops, a comfortable feeling is realized upon the application.

[0026] When CB is incorporated, as the active ingredient, the amount of the oil used is usually 0.5 to 80 parts by weight, preferably 0.5 to 50 parts by, per one part by weight of the phospholipid, and the oil concentration in the emulsion is preferably not higher than 25 w/v%. When the amount of the oil used together with CB is in the range of 0.5 to 80 parts by weight per one part by weight of the phospholipid, the stability of the emulsion during the storage is high and oil drops are not formed during the storage. When the amount of the oil used together with CB is at least 0.5 % by weight per one part by weight of the phospholipid, the color change during the storage is only slight. The oil concentration in the emulsion is preferably 25 w/v% or below because an emulsion having a low viscosity can be obtained, which can be easily administered, and when the emulsion is used as eye drops, a comfortable feeling is realized upon the application.

[0027] In preparing the emulsion of the present invention, additives may be added to the indispensable components, i. e. water, oil or phospholipid so far as the effect of the present invention is not impaired. The additives are isotonicity agents such as sugars, e.g. xylitol, mannitol, sorbitol and glucose, and polyhydric alcohols, e.g. propylene glycol and glycerol; pH adjusting agents such as sodium hydroxide and hydrochloric acid; preservatives such as parabens, e. g. methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, sorbic acid and pharmaceutically acceptable salts thereof, benzyl alcohol, phenethyl alcohol, benzethonium chloride, benzalkonium chloride, chlorhexidine gluconate, hydroxyquinoline sulfate, chlorobutanol and thimerosal; thickening agents such as synthetic polymers, e.g. polyvinylpyrrolidone, polyvinyl alcohol and sodium polyacrylate, high-molecular protein materials, e.g. gelatin, and polysaccharides, e.g. dextran, carrageenan, sodium chondroitin sulfate, xantham gum, gum arabic, Karaya gum and locust bean gum; antioxidants such as ascorbic acid, sodium hydrogensulfite, sodium thioglycolate and α-thioglycerol; and buffering agents such as acetic acid, phosphoric acid and pharmaceutically acceptable salts of them, monoethanolamine, triethanolamine, boric acid, borax, sodium carbonate, sodium hydrogen carbonate, aminoethyl sulfonic acid, ε-aminocaproic acid, sodium chloride and potassium chloride.

[0028] Further, at least one stabilizer selected from the group consisting of amino acids and pharmaceutically acceptable salts thereof, tocopherol and derivatives thereof and sucrose fatty acid esters, can be added to one of the indispensable components, i. e. water, oil and phospholipid, of the present invention.

[0029] Examples of amino acids usable in the present invention include cysteine, histidine, pharmaceutically acceptable salts (such as hydrochlorides) of them, methionine, phenylalanine, serine and the like.

[0030] Examples of the tocopherol derivatives usable in the present invention include tocopherol acetate, tocopherol nicotinate, tocopherol succinate and the like.

[0031] The pH of the emulsion of the present invention is usually controlled in the range of 3 to 10. From the viewpoint of the irritation, the pH range is preferably 5 to 9. When the emulsion is used as eye drops, pH range is preferably 5.5 to 8.0.

[0032] The emulsion of the present invention can be sterilized by the filtration sterilization method with a membrane or by the heating sterilization method.

[0033] The emulsion of the present invention can be filled into a plastic eye drop bottle to use it as eye drops. In order to stably store the emulsion for a long period of time, the emulsion may be packed into a bag made of a laminate of a polyethylene film and an aluminum foil by the pillow type packaging method together with a deoxidizer [such as Ageless (registered trademark) SA, and Ageless Z; Mitsubishi Gas Chemical Co., Ltd.].

[0034] The emulsion of the present invention can be filled into a plastic dropping bottle to use it as ear drops. In order to stably store the emulsion for a long period of time, the emulsion may be packed into a bag made of a laminate of a polyethylene film and an aluminum foil by the pillow type packaging method together with a deoxidizer [such as Ageless (registered trademark) SA, and Ageless Z; Mitsubishi Gas Chemical Co., Ltd.].

[0035] The emulsion of the present invention can be packed into a quantitative nasal nebulizer to use it as nasal drops. In order to stably store the emulsion for a long period of time, the emulsion may be packed into a bag made of a laminate of a polyethylene film and an aluminum foil by the pillow type packaging method together with a disoxidant [such as Ageless (registered trademark) SA, and Ageless Z; Mitsubishi Gas Chemical Co., Ltd.].

[0036] The emulsion of the present invention can be fed into an ampoule and the ampoule is sealed by fusion to obtain an injection (such as intravenous injection, arterial injection, hypodermic injection, intradermal injection, intramuscular injection, intraspinal injection, intraperitoneal injection, intraocular injection and the like), a liquid for internal use, an inhalation or a aerosol. The product thus obtained is fed into a suitable container selected depending on the use, such as a plastic bottle for the liquid for internal use, electric nebulizer for the inhalation, an atomizer for aerosol and the like.

[0037] The description will be made on the methods for preparing the emulsion of the present invention. Various well-known methods can be employed for preparing the emulsion of the present invention. For example, yolk lecithin, if desired a phospholipid such as phosphatidylethanolamine and an emulsifying adjuvant such as oleic acid, and FLM or CB are dissolved in a suitable organic solvent such as hexane or ethanol under stirring. Then, the solvent is evaporated under reduced pressure to prepare a thin lipid membrane. An oil and an aqueous solution prepared by dissolving a non-

ionic, water-soluble cellulose derivative and optionally at least one selected from the group consisting of a chelating agent, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof as well as various additives such as an antiseptic and an isotonicity agent in water, are added to the thin lipid membrane. They are vigorously stirred by agitation to conduct the pre-emulsification. The pre-emulsion thus obtained is emulsified with an ordinary emulsifying machine. After the completion of the emulsification, HCl or NaOH is added to the emulsion to adjust it to an intended pH, and thereby to obtain the O/W emulsion containing FLM or CB of the present invention. The emulsion is filtered and fed into a suitable container through a membrane filter and then sterilized to obtain the emulsion of the present invention.

[0038] When FLM is used as the active ingredient, the intended FLM-containing O/W emulsion of the present invention can be obtained by preparing an O/W emulsion comprising FLM, a phospholipid, an oil and water in the same manner as that described above, adding an aqueous solution containing a nonionic, water-soluble cellulose derivative and optionally at least one of a chelating agent, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof, an antiseptic agent, an isotonicity agent and the like to the emulsion, and stirring the obtained mixture.

Examples

[0039] The following Example will further illustrate the present invention, wherein the emulsion is to be used as eye drops.

Determination of solubility of active ingredient in lachrymal fluid:

[0040] As descried in the above "Background of the Invention", the bioavailability can be improved by increasing the concentration of the administered, hardly soluble active ingredient in the body fluids. In case of eye drops, it is known that the bioavailability can be improved by increasing the concentration of the hardly soluble active ingredient in the lachrymal fluid immediately after the application. The concentration of the active ingredient in the lachrymal fluid can be one of the indexes for determining the degree of improvement in the transfer of the hardly soluble active ingredient into the eye tissue. Because the active ingredient applied to the eye is rapidly excreted from the eye surface which is the main absorption region by the turnover of the lachrymal fluid, etc., a method capable of instantaneously determining the quantity of FLM or CB dissolved in the lachrymal fluid must be employed in the determination of the solubility of FLM or CB in the lachrymal fluid.

[0041] The solubility of FLM or CB in the lachrymal fluid was determined by determining the concentration of FLM or CB dissolved in an artificial lachrymal fluid (PBS) (hereinafter referred to as "FLM dissolution concentration" or "CB dissolution concentration" according to a drug dissolution test method described in "Example" in WO 97/05882, p.10. In the determination of FLM dissolution concentration or CB dissolution concentration, a dilution rate of 1/51 with PBS was selected for the FLM-containing emulsion and that of 1/41 with PBS was selected for CB-containing emulsion on the basis of the dilution rates described in the drug dissolution test method.

Dissolution tests of FLM and CB:

[0042] As the artificial lachrymal fluid used in place of the human lachrymal fluid, PBS usually used for biochemical tests (composition: 0.8 w/v% of NaCl, 0.02 w/v% of KCl, 0.115 w/v% of Na_2HPO_4 and 0.02 w/v% of KH_2PO_4, pH7.4) was used. PBS was fed into a 15 mL test tube with a lid and then kept in a water bath at 36 °C. Then, a predetermined amount of the emulsion was added to PBS, and they were gently and invertibly shaken at room temperature for 30 seconds. The amounts of the emulsion and PBS were as shown below:

Dilution rate	FLM-containing emulsion (mL)	PBS (mL)
1/51	0.1	5.0

Dilution rate	CB-containing emulsion (mL)	PBS (mL)
1/41	0.25	10.0

[0043] PBS (0.4 mL) containing the emulsion was rapidly (within 3 minutes after the addition of the emulsion to PBS) poured in an ultrafiltration kit [Ultrafree (registered trademark)-MC (Cat. No. UFC3LTK00); Millipore Corporation]. Then PBS containing FLM or CB dissolved therein was separated from the emulsion with a centrifugal separator (MS-150; Tomy Seiko Co., Ltd.) (8500 rpm, 5 minutes). The HPLC analysis was used to quantitate FLM or CB present in the separated PBS to determine the dissolution concentration of FLM or CB.

Determination of stability as for solubility of active ingredient in lachrymal fluid and concentration of active ingredient during storage:

[0044] The stability of solubility of each FLM and CB in the lachrymal fluid and the concentration of each FLM and CB during the storage were evaluated as described below.

[0045] 5 mL of a sample was fed into a 5 mL white glass ampoule, which was then sealed by fusion and stored at 40°C or 60°C. After the storage at such a temperature for a predetermined period of time, FLM dissolution concentration, CB dissolution concentration, FLM concentration and CB concentration were determined. When the values obtained after the storage was 90 % or higher based on the values obtained before the storage, the results were evaluated to be stable.

Example 1

[0046] Egg yolk lecithin [Coatsome (registered trademark) NC-10S, 95 % phosphatidyicholine; NOF Corporation; hereinafter referred to as "EPC"] and purified egg yolk lecithin (70 % phosphatidylcholine and 20 % phosphatidylethanolamine; Asahi Chemical Industry Co., Ltd.; hereinafter referred to as "PYL") in a weight ratio of 7:3 were dissolved in a mixture of hexane/ethanol [10/1 (v/v)] under stirring. Separately, FLM was dissolved in ethanol, and the obtained solution was mixed under stirring with the phospholipid solution obtained as described above. Then, the solvent was evaporated with an evaporator and then with a vacuum pump to form a thin phospholipid membrane containing FLM.

[0047] Methylcellulose [Metolose (registered trademark) SM-400 (Shin-Etsu Chemical Co., Ltd.)] or Hydroxypropylmethylcellulose [Metolose (registered trademark) 60SH-4000 (Shin-Etsu Chemical Co., Ltd.)] was dispersed in hot water (70°C or higher) to obtain a hot, homogeneous aqueous slurry, which was then cooled under stirring to obtain a solution Glycerol was dissolved in the resultant solution to obtain an aqueous glycerol solution containing methylcellulose or hydroxypropylmethyl-cellulose.

[0048] The obtained aqueous solution and liquid paraffin (No. 260-S; Sanko Chemical Industry Co. Ltd.) were added to the thin phospholipid membrane prepared as described above, and they were stirred by vigrously shaking to conduct the pre-emulsification. Distilled water was added to the pre-emulsified liquid to make the total amount 100 mL. The obtained mixture was emulsified by passing through a microfluidizer (M-110EH; Microfluidics Co.) 30 times under a pressure of 750 kg/cm^2. After the completion of the emulsification, 1 N NaOH was added to the emulsion to adjust pH thereof to 6.5-7.5 to obtain the FLM-containing O/W emulsion (hereinafter referred to as "FLM emulsion") of the present invention. The formulation of the emulsion is shown in Table 1.

Example 2

[0049] An FLM emulsion of the present invention was obtained in the same manner as that of Example 1 except that EDTA disodium salt or sodium citrate was dissolved, under stirring, in the aqueous glycerol solution containing methylcellulose or hydroxypropylmethylcellulose. The formulation is shown in Table 1.

Comparative Example 1

[0050] An FLM emulsion was obtained in the same manner as that of Example 1 except that methylcellulose and hydroxypropylmethylcellulose were not added. The formulation is shown in Table 1.

Comparative Example 2

[0051] An FLM emulsion was obtained in the same manner as that of Example 2 except that methylcellulose and hydxoxypropylmethylcellulose were not added. The formulation is shown in Table 1.

Table 1

		Phospholipid w/v%	Liquid paraffin w/v%	FLM conc. w/v%	Nonionic water-soluble cellulose derivative w/v%	Polycarboxylic acid compound and chelating agent w/v%
Ex.1	1	2.0	10.0	0.02	MC 0.10	-
	2	2.0	10.0	0.02	HPMC 0.10	-
Ex.2	1	2.0	10.0	0.02	MC 0.10	EDTA 0.05
	2	2.0	10.0	0.02	MC 0.10	Cit 0.10
	3	2.0	10.0	0.02	HPMC 0.10	EDTA 0.05
	4	2.0	10.0	0.02	HPMC 0.10	Cit 0.10
Comp. Ex.1	1	2.0	10.0	0.02	-	-
Comp. Ex.2	1	2.0	10.0	0.02	-	EDTA 0.05
	2	2.0	10.0	0.02	-	Cit 0.10

MC: methylcellulose [Metolose (registered trademark) SM-400 (Shin-Etsu Chemical Co., Ltd.)]
HPMC: hydroxypropylmethylcellulose [Metolose 60SH-4000 (Shin-Etsu Chemical Co., Ltd.)]
Liquid paraffin; Liquid paraffin No. 260-S (Sanko Chemical Industry Co. Ltd.
EDTA: ethylenediaminetetraacetic acid disodium salt
Cit: sodium citrate
Phospholipid: EPC:PYL = 7:3 (weight ratio)
Each formulation contains 2.2 w/v% of glycerol

Test Example 1

[0052] The FLM dissolution tests and tests on the stability of FLM dissolution concentration and of FLM concentration during the storage, of each of the emulsions of the present invention obtained in Examples 1 and 2 and the emulsions obtained in Comparative Examples 1 and 2 were conducted by methods of "Determination of solubility of active ingredient in lachrymal fluid" and "Determination of stability as for solubility of active ingredient in lachrymal fluid and concentration of active ingredient during storage" described above. Table 2 shows the FLM dissolution concentrations in FLM emulsions of the present invention obtained in Examples 1 and 2 and that in FLM emulsions obtained in Comparative Examples 1 and 2, and also the results of the stability test of the emulsions after the storage at 60°C for one and two weeks. For comparison, the FLM dissolution concentrations in commercially available FLM suspensions [Flumetholon (registered trademarks) 0.02 and 0.1; Santen Pharmaceutical Co., Ltd.] are also shown.

[0053] The FLM emulsions of the present invention have remarkably higher FLM dissolution concentrations than those obtained in Comparative Examples. The FLM dissolution concentration and FLM concentration were stable after the storage at 60°C for one week. Particularly, the FLM emulsions of the present invention containing EDTA disodium salt or sodium citrate were stable on FLM dissolution concentration and FLM concentration even after the storage at 60°C for two weeks.

Table 2

		FLM dissolution conc. μg/ml	Storage stability			
			Storage (60°C, 1 week)		Storage (60°C, 2 weeks)	
			FLM cone.	FLM dissolution conc.	FLM conc.	FLM dissolution conc.
Ex.1	1	2.42	○	○	○	X
	2	2.54	○	○	○	X
Ex.2	1	2.44	○	○	○	○
	2	2.45	○	○	○	○
	3	2.48	○	○	○	○
	4	2.57	○	○	○	○
Comp.Ex.1		1.62	X	X	X	X
Comp. Ex.2	1	2.02	○	X	X	X
	2	2.08	X	X	X	X
Suspension (Flumetholon 0.02)		0.73	-	-	-	-
Suspension (Flumetholon 0.1)		1.54	-	-	-	-

Dissolution test: FLM emulsion was diluted to a concentration of 1/51 with PBS.
Storage stability:
○ : stable (at least 90 % based on the value before the storage);
X : unstable (less than 90% based on the value before the storage)
Suspension: Flumetholon (registered trademarks) 0.02 and 0.1 (FLM suspended eye drop, 0.02 and 0.1 w/v% FLM, Santen Pharmaceutical Co., Ltd.).

Example 3

[0054] An FLM emulsion of the present invention was prepared in the same manner as that of Example 2 except that Liquid paraffin No. 200-S (Sanko Chemical Industry Co. Ltd.) was used as an oil and Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose. The formulation is shown in Table 3.

Comparative Example 3

[0055] An FLM emulsion was prepared in the same manner as that of Example 3 except that methylcellulose was not used. The formulation is shown in Table 3.

Table 3

	Phospholipid w/v%	Liquid paraffin w/v%	FLM conc. w/v%	Methylcellulose w/v%	EDTA w/v%
Ex.3	9.0	25.0	0.1	0.5	0.008

Table 3 (continued)

	Phospholipid w/v%	Liquid paraffin w/v%	FLM conc. w/v%	Methylcellulose w/v%	EDTA w/v%
Comp.Ex.3	9.0	25.0	0.1	-	-
Liquid paraffin: Liquid paraffin No. 200-S (Sanko Chemical Industry Co. Ltd.) Methylcellulose: Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.) EDTA: ethylenediaminetetraacetic acid disodium salt Phospholipid: EPC:PYL = 7:3 (weight ratio) Each formulation contains 2.0 w/v% of glycerol					

Test Example 2

[0056] The FLM dissolution tests and tests on the stability of FLM dissolution concentration and of FLM concentration during the storage of the FLM emulsion of the present invention obtained in Example 3 and the FLM emulsion of Comparative Example 3 were conducted in the same manner as that of Test Example 1. Table 4 shows the dissolution concentrations of the FLM emulsion of the present invention obtained in Example 3 and the FLM emulsion obtained in Comparative Example 3 and also the results of the stability test of the emulsions obtained after the storage at 40°C for four weeks. For comparison, the FLM dissolution concentration of the commercially available FLM suspension [Flumetholon (registered trademarks) 0.1; Santen Pharmaceutical Co., Ltd.] is also shown.

[0057] The FLM emulsion of the present invention had a remarkably higher FLM dissolution concentration than that obtained in the Comparative Example. The FLM dissolution concentration and FLM concentration were stable after the storage at 40°C for four weeks.

Table 4

	FLM dissolution conc. μg/ml	Storage stability (40°C, 4 weeks)	
		FLM conc.	FLM dissolution conc.
Ex.3	6.71	○	○
Comp.Ex.3	4.40	○	X
Suspension (Flumetholon 0.1)	1.54	-	-
Dissolution test: FLM emulsion was diluted to a concentration of 1/51 with PBS. Storage stability: ○ : stable (at least 90 % based on the value before the storage); X : unstable (less than 90% based on the value before the storage) Suspension: Flumetholon (registered trademarks) 0.1 (FLM suspended eye drop, 0.1 w/v% FLM, Santen Pharmaceutical Co., Ltd.).			

Example 4

[0058] An FLM emulsion of the present invention comprising FLM, a phospholipid. (weight ratio of EPC:PYL = 7:3), liquid paraffin (No. 150-S; Sanko Chemical Industry Co. Ltd.), soybean oil (Wako Pure Chemical Industries, Co., Ltd.), Panasate 810 (NOF Corporation), corn oil (SIGMA Chemical Company) or tricaprylin (Wako Pure Chemical Industries, Co., Ltd.) as the oils, methylcellulose [Metolose (registered trademark) SM-100; Shin-Etsu Chemical Co., Ltd.], EDTA disodium salt, glycerol and water was prepared in the same manner as that of Example 2. The formulation is shown in Table 5.

Table 5

		Phospholipid w/v%	Oil w/v%		FLM conc. w/v%	Methylcellulose w/v%	EDTA w/v%
Ex.4	1	1.4	Liquid paraffin	7.0	0.02	0.1	0.01
	2	1.4	Soybean oil	7.0	0.02	0.1	0.01
	3	1.4	Panasate8	7.0	0.02	0.1	0.01
	4	1.4	Corn oil	7.0	0.02	0.1	0.01
	5	1.4	Tricaprylin	7.0	0.02	0.1	0.01

Liquid paraffin: Liquid paraffin No. 150-S (Sanko Chemical Industry Co. Ltd.
Soybean oil: Wako, the first grade (Wako Pure Chemical Industries, Co., Ltd.)
Panasate 810: medium chain fatty acid triglyceride (NOF Corporation)
Corn oil: SIGMA CHEMICAL COMPANY
Tricaprylin (Wako Pure Chemical Industries, Co., Ltd.)
Methylcellulose: Metolose SM-100 (Shin-Etsu Chemical Co., Ltd.)
EDTA: ethylenediaminetetraacetic acid disodium salt
Phospholipid: EPC:PYL = 7:3 (weight ratio)
Each formulation contains 2.2 w/v% of glycerol

Test Example 3

[0059] The FLM dissolution tests and tests on the stability of FLM dissolution concentration and of FLM concentration during the storage of the FLM emulsion of the present invention obtained in Example 4 were conducted in the same manner as that of Test Example 1. Table 6 shows the FLM dissolution concentrations of the FLM emulsion of the present invention obtained in Example 4 and also the results of the stability test after the storage at 60°C for two weeks.

[0060] All the FLM emulsions of the present invention obtained by using various oils had high FLM dissolution concentrations. The FLM dissolution concentration and FLM concentration were stable after the storage at 60°C for two weeks.

Table 6

		FLM dissolution conc. μg/ml	Storage stability (60°C, 2 weeks)	
			FLM conc.	FLM dissolution conc.
Ex.4	1	3.33	○	○
	2	2.79	○	○
	3	2.69	○	○
	4	2.81	○	○
	5	2.67	○	○

Dissolution test: FLM emulsion was diluted to a concentration of 1/51 with PBS.
Storage stability:
○ : stable (at least 90 % based on the value before the storage);
X : unstable (less than 90% based on the value before the storage)

Example 5

[0061] An FLM emulsion of the present invention comprising FLM, a phospholipid (weight ratio of EPC:PYL = 7:3), liquid paraffin (No. 150-S; Sanko Chemical Industry Co. Ltd.), methylcellulose [Metolose (registered trademark) SM-

100; Shin-Etsu Chemical Co., Ltd.], EDTA disodium salt, glycerol and water was prepared in the same manner as that of Example 2. The formulation is shown in Table 7.

Table 7

		Phospholipid w/v%	Liquid paraffin w/v%	FLM conc. w/v%	Lip/FLM	LP/Lip	Methylcellulose w/v%	EDTA w/v%
Ex.2	1	2.0	10.0	0.02	100	5	0.1	0.05
Ex.4	1	1.4	7.0	0.02	70	5	0.1	0.01
Ex.5	1	0.2	0.2	0.005	40	1	0.01	0.0004
	2	1.4	7.0	0.02	70	5	0.001	0.05
	3	1.4	7.0	0.02	70	5	0.5	0.18

Liquid paraffin: Liquid paraffin No. 150-S (Sanko Chemical Industry Co. Ltd.)
Lip/FLM: phospholipid (w/v%) / FLM (w/v%)
LP/Lip: liquid paraffin (w/v%) / phospholipid (w/v%)
Methylcellulose: Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.)
EDTA: ethylene diaminetetraacetic acid disodium salt
Phospholipid: EPC:PYL = 7:3 (weight ratio)
Each formulation contains 2.2 w/v% of glycerol

Test Example 4

[0062] The FLM dissolution tests and tests on the stability of FLM dissolution concentration and of FLM concentration during the storage of the FLM emulsion of the present invention obtained in Example 5 were conducted in the same manner as that of Test Example 1. Table 8 shows the FLM dissolution concentrations of the FLM emulsions of the present invention obtained in Examples 2-1, 4-1 and 5 and also the results of the stability test obtained after the storage at 60°C for two weeks.

[0063] All the FLM emulsions of the present invention containing 0.001 to 0.5 w/v% of methylcellulose and 0.0004 to 0.18 w/v% of EDTA disodium salt had high FLM dissolution concentrations. The FLM dissolution concentration and FLM concentration were stable after the storage at 60°C for two weeks.

Table 8

		FLM dissolution cone. μg/ml	Storage stability (60°C, 2 weeks)	
			FLM conc.	FLM dissolution conc.
Ex.2	1	2.44	○	○
Ex.4	1	3.33	○	○
Ex.5	1	0.76	○	○
	2	1.98	○	○
	3	2.61	○	○

Dissolution test: FLM emulsion was diluted to a concentration of 1/51 with PBS.
Storage stability:
○ : stable (at least 90 % based on the value before the storage);
X : unstable (less than 90% based on the value before the storage)

Example 6

[0064] A CB-containing O/W emulsion of the present invention (hereinafter referred to as "CB emulsion"), a phos-

pholipid (weight ratio of EPC:PYL = 7:3), liquid paraffin (No. 150-S; Sanko Chemical Industry Co. Ltd.), methylcellulose [Metolose (registered trademark) SM-100; Shin-Etsu Chemical Co., Ltd.], glycerol and water was prepared in the same manner as that of Example 1. The formulation is shown in Table 9.

Example 7

[0065] A CB-containing O/W emulsion of the present invention comprising CB, a phospholipid (weight ratio of EPC:PYL = 7:3), liquid paraffin (No. 150-S; Sanko Chemical Industry Co. Ltd.), methylcellulose [Metolose (registered trademark) SM-100; Shin-Etsu Chemical Co., Ltd.], EDTA disodium salt, glycerol and water was prepared in the same manner as that of Example 2. The formulation is shown in Table 9.

Comparative Example 4

[0066] A CB emulsion was prepared in the same manner as that of Example 6 except that methylcellulose was not added. The formulation is shown in Table 9.

Comparative Example 5

[0067] A CB emulsion was prepared in the same manner as that of Example 7 except that methylcellulose was not added. The formulation is shown in Table 9.

Table 9

		Phospholipid w/v%	Liquid paraffin w/v%	CB conc. w/v%	Methylcellulose w/v%	EDTA w/v%
Ex.6		0.84	4.2	0.018	0.2	-
Ex.7	1	0.84	4.2	0.018	0.2	0.01
	2	0.2	9.0	0.02	0.1	0.01
Comp.Ex.4		0.84	4.2	0.018	-	-
Comp.Ex.5		0.84	4.2	0.018.	-	0.01

Liquid paraffin: Liquid paraffin No. 150-S (Sanko Chemical Industry Co. Ltd.
Methylcellulose: Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.)
EDTA: ethylenediaminetetraacetic acid disodium salt
Phospholipid: EPG:PYL = 7:3 (weight ratio)
Each formulation contains 2.2 w/v% of glycerol

Test Example 5

[0068] The CB dissolution tests and tests on the stability of CB dissolution concentration and on the stability of CB concentration during the storage of the CB emulsions of the present invention obtained in Examples 6 and 7 and Comparative Examples 4 and 5 were conducted in the same manner as that of Test Example 1. Table 10 shows the CB dissolution concentrations of the CB emulsions of the present invention obtained in Examples 6 and 7 and Comparative Examples 4 and 5 and also the results of the stability test after the storage at 40°C for four weeks and 24 weeks. For comparison, the CB dissolution concentration of a commercially available CB suspension [CLOBURATE (registered trademark), 0.1 w/v% CB, Cusi (UK) Ltd.] was also shown.

[0069] All the CB emulsions of the present invention had high CB dissolution concentrations. The CB dissolution concentration and CB concentration were stable after the storage at 40°C for 4 weeks. Particularly, the CB dissolution concentration and CB concentration of the CB emulsion of the present invention containing EDTA disodium salt were stable after the storage at 40°C for 24 weeks.

Table 10

		CB dissolution conc. μg/ml	Storage stability			
			Storage (40°C, 4 weeks)		Storage (40°C, 24 weeks)	
			CB conc.	CB dissolution conc.	CB conc.	CB dissolution conc.
Ex.6		0.40	○	○	X	X
Ex.7	1	0.39	○	○	○	○
	2	0.36	○	○	○	○
Comp.Ex.4		0.31	○	X	X	X
Comp. Ex.5		0.25	○	X	X	X
Suspension		0.17	-	-	-	-

Dissolution test: CB emulsion was diluted to a concentration of 1/41 with PBS.
Storage stability:
○ : stable (at least 90 % based on the value before the storage);
X : unstable (less than 90% based on the value before the storage)
Suspension: CLOBURATE (registered trademark), [CB-suspended eye drop, 0.1 w/v% CB, Cusi (UK) Ltd.]

Preparation Example 1

[0070] EPC, PYL and α-tocopherol acetate were dissolved in a mixture of hexane/ethanol [10/1 (v/v)] under stirring. Separately, FLM was dissolved in ethanol, and the obtained solution was mixed with the phospholipid solution, obtained as described above, under stirring. The solvent was evaporated with an evaporator and then with a vacuum pump to form a thin phospholipid membrane containing FLM.

[0071] Methylcellulose [Metolose (registered trademark) SM-400; Shin-Etsu Chemical Co., Ltd.] was dispersed in hot water (70°C or higher) to obtain a hot homogeneous aqueous slurry, which was then cooled under stirring to obtain a solution. Polyvinylpyrrolidone [Kollidone (registered trademark) 30, BASF Aktiengesellschaft], glycerol, potassium sorbate and EDTA disodium salt were dissolved in the solution under stirring to obtain a solution of the water-soluble components.

[0072] The obtained solution of the water-soluble components and liquid paraffin (No. 260-S; Sanko Chemical Industry Co. Ltd.) were added to the thin phospholipid membrane prepared as described above, and they were vigorously shaken to conduct the pre-emulsification. Distilled water was added to the pre-emulsified liquid to make the total quantity 1 L. The obtained mixture was emulsified by passing through a microfluidizer (M-110EH; Microfluidics Co.) 30 times under a pressure of 750 kg/cm^2. After the completion of the emulsification, 1 N NaOH was added to the emulsion to adjust pH thereof to 6.0. The emulsion was filtered through a membrane having a pore diameter of 0.45 μm to obtain an FLM emulsion of the present invention containing the above-described additives. The emulsion was fed into an eye drop bottle and sterilized by heating by the intermittent sterilization method to obtain the FLM-containing eye drops of the present invention. The eye drops of the present invention thus obtained were packed in a polyethylene film/aluminum foil laminate bag together with Ageless (registered trademark) Z (Mitsubishi Gas Chemical Co., Inc.) by the pillow type packaging method. The formulation was as follows:

Preparation 1

[0073]

Component	Amount and concentration
FLM	0.02 w/v%

(continued)

Component	Amount and concentration
EPC	0.98 w/v%
PYL	0.42 w/v%
α-Tocopherol acetate	0.065 w/v%
Liquid paraffin No. 260-S	7.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Polyvinylpyrrolidone	0.05 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 6.0)
Distilled water	ad 1 L

Preparation Example 2

[0074] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Preparation Example 1 except that α-tocopherol acetate was not used, PCSH (hydrogenated soybean phosphatidyl choline; Nippon Fine Chemical Co., Ltd.) was further added as phospholipid and liquid paraffin No. 150-S (Sanko Chemical Industry Co. Ltd.) was used as oil. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 2

[0075]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
PYL	0.42 w/v%
PCSH	0.14 w/v%
Liquid paraffin No. 150-S	7.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Polyvinylpyrrolidone	0.05 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.2 w/v%
1 N HCl	suitable amount (added after emulsification to adjust pH at 5.5)
Distilled water	ad 1 L

Preparation Example 3

[0076] FLM-containing eye drops of the present invention were prepared in the same manner, as that of the emulsion preparation method of Preparation Example 1 except that α-tocopherol acetate was not used, Coatsome (regis-

tered trademark) MC-6060 (L-α-dipalmitoyl phosphatidylcholine; NOF Corporation) was further added as the phospholipid, liquid paraffin No. 350-S (Sanko Chemical Industry Co. Ltd.) was used as oil and polyvinylpyrrolidone was replaced with gelatin (BACTO GELATIN; DIFCO LABORATORIES). The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 3

[0077]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
Coatsome (registered trademark) MC-6060	0.14 w/v%
PYL	0.42 w/v%
Liquid paraffin No. 350-S	7.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Gelatin	0.05 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.2 w/v%
1 N HCl	suitable amount (added after emulsification to adjust pH at 5.0)
Distilled water	ad 1 L

Preparation Example 4

[0078] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Preparation Example 1 except that α-tocopherol acetate was not used, Coatsome (registered trademark) NC-21 (hydrogenated soybean lecithin; NOF Corporation) was further added as the phospholipid, light liquid paraffin No. 70-S (Sanko Chemical Industry Co. Ltd.) was used as oil, Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose, polyvinylpyrrolidone was replaced with a polyvinyl alcohol (degree of polymerization: about 2,000; Wake Pure Chemical Industries, Co., Ltd.) and potassium sorbate was replaced with benzyl alcohol. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 4

[0079]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
Coatsome (registered trademark) NC-21	0.14 w/v%
PYL	0.42 w/v%
Light liquid paraffin No. 70-S	7.0 w/v%
Metolose (registered trademark) SM-100	0.1 w/v%

(continued)

Component	Amount and concentration
Disodium EDTA	0.01 w/v%
Polyvinyl alcohol	0.05 w/v%
Benzyl alcohol	0.5 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.0)
Distilled water	ad 1 L

Preparation Example 5

[0080] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Preparation Example 1 except that α-tocopherol acetate was not used, egg yolk lecithin LPL-20 (Q. P. Corporation) was further added as the phospholipid, Metolose (registered trademark) SM-1500 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose and potassium sorbate was replaced with benzyl alcohol. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 5

[0081]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
Egg yolk lecithin LPL-20	0.14 w/v%
PYL	0.42 w/v%
Liquid paraffin No. 260-S	7.0 w/v%
Metolose (registered trademark) SM-1500	0.1 w/v%
Disodium EDTA	0.01 w/v%
Polyvinylpyrrolidone	0.05 w/v%
Benzyl alcohol	0.5 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.5)
Distilled water	ad 1 L

Preparation Example 6

[0082] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Preparation Example 1 except that α-tocopherol acetate was not used, oleic acid was dissolved in the phospholipid solution by stirring, Metolose (registered trademark) SM-25 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose, polyvinylpyrrolidone was replaced with sodium polyacrylate (degree of polymerization: 22,000 to 70,000, high viscosity; Wako Pure Chemical Industries, Co., Ltd.), potassium sorbate was replaced with phenethyl alcohol and glycerol was replaced with propylene glycol. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 6

[0083]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
PYL	0.42 w/v%
Oleic acid	0.07 w/v%
Liquid paraffin No. 260-S	7.0 w/v%
Metolose (registered trademark) SM-25	0.1 w/v%
Disodium EDTA	0.01 w/v%
Sodium polyacrylate	0.05 w/v%
Phenethyl alcohol	0.4 w/v%
Propylene glycol	2.0 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 8.0)
Distilled water	ad 1 L

Preparation Example 7

[0084] Methylcellulose [Metolose (registered trademark) SM-400; Shin-Etsu Chemical Co., Ltd.] was dispersed in hot water (70°C or higher) to obtain a homogeneous hot aqueous slurry, which was then cooled under stirring to obtain a solution. Propylene glycol, histidine, sodium citrate and chlorobutanol were dissolved in the solution under stirring to obtain a solution of the water-soluble components.

[0085] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Preparation Example 1 except that α-tocopherol acetate was not used and the solution of water-soluble components described above was used in place of the solution used in Preparation Example 1. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 7

[0086]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
PYL	0.42 w/v%
Liquid paraffin No. 260-S	7.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Sodium citrate	0.075 w/v%
Histidine	0.02 w/v%
Chlorobutanol	0.25 w/v%
Propylene glycol	2.0 w/v%

(continued)

Component	Amount and concentration
1 N HCl	suitable amount (added after emulsification to adjust pH at 6.0)
Distilled water	ad 1 L

Preparation Example 8

[0087] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Preparation Example 1 except that α-tocopherol acetate was not used, cholesterol was further dissolved in the phospholipid solution under stirring, polyvinylpyrrolidone was replaced with dextran (Dextran T70; Pharmacia Fine chemicals), potassium sorbate was replaced with chlorohexidine gluconate and glycerol was replaced with sorbitol. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 8

[0088]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
PYL	0.42 w/v%
Cholesterol	0.1 w/v%
Liquid paraffin No. 260-S	7.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Dextran T70	0.05 w/v%
Chlorohexidine gluconate	0.05 w/v%
Sorbitol	5.0 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.5)
Distilled water	ad 1 L

Preparation Example 9

[0089] Methylcellulose [Metolose (registered trademark) SM-400; Shin-Etsu Chemical Co., Ltd.] was dispersed in hot water (70°C or higher) to obtain a homogeneous hot aqueous slurry, which was then cooled under stirring to obtain a solution. Methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, a sucrose oleic acid ester (Ryoto Sugar ester O-1570; Mitsubishi Chemical Co. Ltd.), EDTA disodium salt and glycerol were dissolved in the solution under stirring to obtain a solution of the water-soluble components.

[0090] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Example 1 except that α-tocopherol acetate was not used, palmitic acid was further dissolved in the phospholipid solution by stirring, and a solution of the water-soluble components was replaced for the above-described solution. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 9

[0091]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
PYL	0.42 w/v%
Palmitic acid	0.14 w/v%
Liquid paraffin No. 260-S	7.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Ryoto Sugar Ester O-1570	0.05 w/v%
Methyl p-hydroxybenzoate	0.026 w/v%
Propyl p-hydroxybenzoate	0.014 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.0)
Distilled water	ad 1 L

Preparation Example 10

[0092] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Example 1 except that α-tocopherol acetate was not used, liquid paraffin No. 70-S (Sanko Chemical Industry Co. Ltd.) was used as oil, polyvinylpyrrolidone was replaced with sodium polyacrylate (degree of polymerization: 22,000 to 70,000, high viscosity; Wako Pure Chemical Industries, Co., Ltd.) and potassium sorbate was replaced with thimerosal. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 10

[0093]

Component	Amount and concentration
FLM	0.02 w/v%
EPC	0.98 w/v%
PYL	0.42 w/v%
Light liquid paraffin No. 70-S	7.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Sodium polyacrylate	0.05 w/v%
Thimerosal	0.01 w/v%
Glycerol	2.2 w/v%

(continued)

Component	Amount and concentration
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.0)
Distilled water	ad 1 L

Preparation Example 11

[0094] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Example 1 except that α-tocopherol acetate was not used, light liquid paraffin No. 200-S (Sanko Chemical Industry Co. Ltd.) was used as oil, Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose, polyvinylpyrrolidone was replaced with sodium polyacrylate (degree of polymerization: 22,000 to 70,000, high viscosity; Wako Pure Chemical Industries, Co., Ltd.) and potassium sorbate was replaced with benzalkonium chloride. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 11

[0095]

Component	Amount and concentration
FLM	0.01 w/v%
EPC	0.56 w/v%
PYL	0.24 w/v%
Light liquid paraffin No. 200-S	4.0 w/v%
Metolose (registered trademark) SM-100	1.0 w/v%
Disodium EDTA	0.01 w/v%
Sodium polyacrylate	0.05 w/v%
Benzalkonium chloride	0.005 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.0)
Distilled water	ad 1 L

Preparation Example 12

[0096] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Example 1 except that α-tocopherol acetate was not used, light liquid paraffin No. 200-S (Sanko Chemical Industry Co. Ltd.) was used as the oil, Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose, polyvinylpyrrolidone was replaced with sodium polyacrylate (degree of polymerization: 22,000 to 70,000, high viscosity; Wako Pure Chemical Industries, Co., Ltd.) and potassium sorbate was replaced with hydroxyquinoline sulfate. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 12

[0097]

Component	Amount and concentration
FLM	0.01 w/v%
EPC	0.56 w/v%
PYL	0.24 w/v%
Light liquid paraffin No. 200-S	4.0 w/v%
Metolose (registered trademark) SM-100	0.5 w/v%
Disodium EDTA	0.01 w/v%
Sodium polyacrylate	0.02 w/v%
Hydroxyquinoline sulfate	0.01 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.0)
Distilled water	ad 1 L

Preparation Example 13

[0098] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Example 1 except that α-tocopherol acetate was not used, light liquid paraffin No. 200-S (Sanko Chemical Industry Co. Ltd.) was used as oil and Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 13

[0099]

Component	Amount and concentration
FLM	0.05 w/v%
EPC	2.8 w/v%
PYL	1.2 w/v%
Light liquid paraffin No. 200-S	16.0 w/v%
Metolose (registered trademark) SM-100	0.1 w/v%
Disodium EDTA	0.01 w/v%
Polyvinylpyrrolidone	0.02 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.0 w/v%
1 N HCl	suitable amount (added after emulsification to adjust pH at 7.0)
Distilled water	ad 1 L

Preparation Example 14

[0100] FLM-containing eye drops of the present invention were prepared in the same manner as that of the emulsion preparation method of Example 1 except that α-tocopherol acetate and polyvinylpyrrolidone were not used, liquid paraffin No. 200-S (Sanko Chemical Industry Co. Ltd.) was used as the oil and Metolose (registered trademark) SM-100 (Shin-Etsu Chemical Co., Ltd.) was used as methylcellulose. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 14

[0101]

Component	Amount and concentration
FLM	0.1 w/v%
EPC	6.3 w/v%
PYL	2.7 w/v%
Liquid paraffin No. 200-S	25.0 w/v%
Metolose (registered trademark) SM-100	0.5 w/v%
Disodium EDTA	0.008 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.0 w/v%
1 N HCl	suitable amount (added after emulsification to adjust pH at 5.5)
Distilled water	ad 1 L

Preparation Example 15

[0102] CB-containing eye drops of the present invention were prepared in the same manner as that of Preparation Example 1 except that CB was replaced for FLM. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 15

[0103]

Component	Amount and concentration
CB	0.02 w/v%
EPC	0.28 w/v%
PYL	0.12 w/v%
α-Tocopherol acetate	0.016 w/v%
Liquid paraffin No. 260-S	2.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Polyvinylpyrrolidone	0.05 w/v%
Potassium sorbate	0.1 w/v%

(continued)

Component	Amount and concentration
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 6.0)
Distilled water	ad 1 L

Preparation Example 16

[0104] CB-containing eye drops of the present invention were prepared in the same manner as that of Preparation Example 3 except that CB was replaced for FLM. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 16

[0105]

Component	Amount and concentration
CB	0.02 w/v%
EPC	0.21 w/v%
Coatsome (registered trademark) MC-6060	0.03 w/v%
PYL	0.09 w/v%
Liquid paraffin No. 350-S	13.5 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Gelatin	0.05 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 6.0)
Distilled water	ad 1 L

Preparation Example 17

[0106] CB-containing eye drops of the present invention were prepared in the same manner as that of Preparation Example 5 except that CB was replaced for FLM. The product was packed m the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 17

[0107]

Component	Amount and concentration
CB	0.02 w/v%
EPC	0.7 w/v%
Egg yolk lecithin LPL-20	0.1 w/v%

(continued)

Component	Amount and concentration
PYL	0.3 w/v%
Liquid paraffin No. 260-S	1.0 w/v%
Metolose (registered trademark) SM-1500	0.1 w/v%
Disodium EDTA	0.01 w/v%
Polyvinylpyrrolidone	0.05 w/v%
Benzyl alcohol	0.5 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 8.5)
Distilled water	ad 1 L

Preparation Example 18

[0108] CB-containing eye drops of the present invention were prepared in the same manner as that of Preparation Example 10 except that CB was replaced for FLM. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 18

[0109]

Component	Amount and concentration
CB	002 w/v%
EPC	0.21 w/v%
PYL	0.09 w/v%
Light liquid paraffin No. 70-S	13.5 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Sodium polyacrylate	0.05 w/v%
Thimerosal	0.01 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.0)
Distilled water	ad 1 L

Preparation Example 19

[0110] CB-containing eye drops of the present invention were prepared in the same manner as that of Preparation Example 1 except that CB was replaced for FLM. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 19

[0111]

Component	Amount and concentration
CB	0.002 w/v%
EPC	0.07 w/v%
PYL	0.03 w/v%
α-Tocopherol acetate	0.004 w/v%
Liquid paraffin No. 260-S	0.1 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Polyvinylpyrrolidone	0.05 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 6.0)
Distilled water	ad 1 L

Preparation Example 20

[0112] CB-containing eye drops of the present invention were prepared in the same manner as that of Preparation Example 3 except that CB was replaced for FLM. The product was packed in the same manner as that of Preparation Example 1. The formulation was as follows:

Preparation 20

[0113]

Component	Amount and concentration
CB	0.05 w/v%
EPC	0.7 w/v%
Coatsome (registered trademark) MC-6060	0.1 w/v%
PYL	0.3 w/v%
Liquid paraffin No. 350-S	15.0 w/v%
Metolose (registered trademark) SM-400	0.1 w/v%
Disodium EDTA	0.01 w/v%
Gelatin	0.05 w/v%
Potassium sorbate	0.1 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 6.0)
Distilled water	ad 1 L

Preparation Example 21

[0114] The FLM-containing emulsion of the present invention produced in Preparation Example 13 was fed into a quantitative nasal aerosol and heat-sterilized by the intermittent sterilization method to obtain nasal drops.

Preparation Example 22

[0115] The FLM-containing emulsion of the present invention produced in Preparation Example 13 was fed into a dropping bottle and heat-sterilized by the intermittent sterilization method to obtain ear drops.

Preparation Example 23

[0116] The FLM-containing emulsion of the present invention produced in Preparation Example 13 was heat-sterilized by the intermittent sterilization method and then fed into an electric nebulizer to obtain an inhalation.

Preparation Example 24

[0117] The FLM-containing emulsion of the present invention produced in Preparation Example 13 was heat-sterilized by the intermittent sterilization method and then fed into an atomizer to obtain an aerosol.

Preparation Example 25

[0118] The FLM-containing emulsion of the present invention produced in Preparation Example 13 was fed into an ampoule, and the ampoule was sealed. After the heat-sterilization by the intermittent sterilization method, a liquid for internal use was obtained.

Preparation Example 26

[0119] EPC and PYL were dissolved in a mixture of hexane/ethanol [10/1 (v/v)] under stirring. Separately, FLM was dissolved in ethanol, and the obtained solution was mixed with the phospholipid solution, obtained as described above, under stirring. The solvent was evaporated with an evaporator and then with a vacuum pump to form a thin phospholipid membrane containing FLM.

[0120] Methylcellulose [Metolose (registered trademark) SM-100; Shin-Etsu Chemical Co., Ltd.] was dispersed in hot water (water for injection, 70°C or higher) to obtain a homogeneous hot aqueous slurry, which was then cooled under stirring to obtain a solution. Glycerol and sodium citrate were dissolved in the solution under stirring to obtain a solution of these water-soluble components.

[0121] The obtained solution of the water-soluble components and liquid paraffin (No. 260-S; Sanko Chemical Industry Co. Ltd.) were added to the thin phospholipid membrane prepared as described above, and they were vigorously shaken to conduct the pre-emulsification. Water for injection was added to the pre-emulsified liquid to make the total amount 1 L. The obtained mixture was emulsified by passing through a microfluidizer (M-110EH; Microfluidics Co.) 30 times under a pressure of 740 kg/cm^2. After the completion of the emulsification, 1 N NaOH was added to the emulsion to adjust pH thereof to 7.4. The emulsion was filtered through a membrane having a pore diameter of 0.45 μm to obtain an FLM emulsion of the present invention containing the above-described additives. The emulsion was fed into an ampoule, which was then sealed. The emulsion in the ampoule was sterilized by heating by the intermittent sterilization method to obtain the FLM-containing injection of the present invention. The formulation was as follows:

Preparation 26

[0122]

Component	Amount and concentration
FLM	0.05 w/v%
EPC	2.8 w/v%
PYL	1.2 w/v%

(continued)

Component	Amount and concentration
Liquid paraffin No. 200-S	16.0 w/v%
Metolose (registered trademark) SM-100	0.1 w/v%
Sodium citrate	0.01 w/v%
Glycerol	2.0 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.4)
Water for injection	ad 1 L

Preparation Example 27

[0123] The CB-containing emulsion of the present invention produced in Preparation Example 20 was fed into a quantitative nasal aerosol and heat-sterilized by the intermittent sterilization method to obtain nasal drops.

Preparation Example 28

[0124] The CB-containing emulsion of the present invention produced in Preparation Example 20 was fed into a dropping bottle and heat-sterilized by the intermittent sterilization method to obtain ear drops.

Preparation Example 29

[0125] The CB-containing emulsion of the present invention produced in Preparation Example 20 was heat-sterilized by the intermittent sterilization method and then fed into an electric nebulizer to obtain an inhalation.

Preparation Example 30

[0126] The CB-containing emulsion of the present invention produced in Preparation Example 20 was heat-sterilized by the intermittent sterilization method and then fed into an atomizer to obtain an aerosol.

Preparation Example 31

[0127] The CB-containing emulsion of the present invention produced in Preparation Example 20 was fed into an ampoule, and the ampoule was sealed. After the heat-sterilization by the intermittent sterilization method, a drug for internal use was obtained.

Preparation Example 32

[0128] A CB emulsion of the present invention was prepared in the same manner as that of Example 26. The emulsion was fed into an ampoule. After the heat-sterilization by the intermittent sterilization method, a CB-containing injection of the present invention was obtained. The formulation was as follows:

Preparation 32

[0129]

Component	Amount and concentration
CB	0.05 w/v%
EPC	0.7 w/v%
PYL	0.3 w/v%

(continued)

Component	Amount and concentration
Liquid paraffin No. 200-S	15.0 w/v%
Metolose (registered trademark) SM-100	0.1 w/v%
Sodium citrate	0.01 w/v%
Glycerol	2.2 w/v%
1 N NaOH	suitable amount (added after emulsification to adjust pH at 7.4)
Water for injection	ad 1 L

Industrial Applicability

[0130] The O/W emulsion composition of the present invention has advantages that fluorometholone or clobetasone butyrate contained therein is highly soluble in body fluids such as blood and lachrymal fluid and that the solubility and concentration of fluorometholone or clobetasone butyrate contained in the composition are excellent. Thus, in the treatment of various inflammatory diseases by the generalized or local administration of fluorometholone or clobetasone butyrate, the bioavailability of such an active ingredient can be improved and a high anti-inflammatory activity is expected. In the ophthalmic field, an anti-inflammatory activity equal or higher than that of a commercially available aqueous fluorometholone suspension or also a commercially available aqueous clobetasone butyrate suspension is expectable when it is administered in a dose smaller than that of such a suspension. Further, apprehension of systemic side effects of fluorometholone or clobetasone butyrate administered to the eyes can be relieved. Thus, the preparation excellent in the economization and storability can be provided by the present invention.

Claims

1. An O/W emulsion composition comprising the following components A to E:

   A. fluorometholone or clobetasone butyrate,
   B. a phospholipid,
   C. an oil,
   D. a nonionic water-soluble cellulose derivative, and
   E. a suitable amount of water.

2. The O/W emulsion composition of claim 1, wherein D is methylcellulose and/or hydroxypropylmethylcellulose.

3. The O/W emulsion composition of claim 1 or 2, wherein C is liquid paraffin.

4. The O/W emulsion composition as defined in any one of claims 1 to 3, which further contains:

   F. At least one member selected from the group consisting of chelating agents, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof.

5. The O/W emulsion composition of claim 4, wherein F is at least one member selected from the group consisting of ethylenediaminetetraacetic acid, citric acid and pharmaceutically acceptable salts thereof.

6. The O/W emulsion composition as defined in any one of claims 1 to 5, which contains 0.0005 to 5 w/v% of a nonionic, water-soluble cellulose derivative.

7. The O/W emulsion composition as defined in any one of claims 4 to 6, which contains 0.0001 to 0.2 w/v% of at least one member selected from the group consisting of chelating agents, polycarboxylic acid compounds and pharmaceutically acceptable salts thereof.

8. The O/W emulsion composition as defined in any one of claims 1 to 7, which further contains at least one member selected from the group consisting of isotonicity agents, buffering agents, thickening agents, pH adjusting agents, antioxidants and preservatives.

9. The O/W emulsion composition as defined in any one of claims 1 to 8, which is to be administered in the form of any of liquids for internal use, injections, ear drops, nasal drops, eye drops, aerosols and inhalations.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 60-199833, A (Meiji Milk Products Co., Ltd.), 9 October, 1985 (09. 10. 85) (Family: none)	1-9
A	JP, 9-255529, A (Shiseido Co., Ltd.), 30 September, 1997 (30. 09. 97) (Family: none)	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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(54) Title: POLYMERIC DIFFUSION MATRIX CONTAINING 5-[(3,4-DIMETHOXYPHENETHYL)METHYLAMINO]-2-(3,4-DIMETHOXYPHENYL)-2-ISOPROPYLVALERONITRILE

(57) Abstract

A self-supporting polymeric diffusion matrix for the sustained release of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile in order to deliver the 5-[D(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to a patient and to provide the patient with an anti-anginal effect and with relief from other heart disorders. The matrix comprises from about 1 to about 60 % of a polar plasticizer, from about 6 to about 30 % by weight polyvinylalcohol, from about 2 to about 30 % by weight polyvinylpyrrolidone, and about 2 to 5 % of the 5-[(3,4-dimethoxyphenethyl)methylamino]D-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to provide a sustained release of said 5[(3,4-dimethoxyphenethyl)methylamino]BD-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile over a prolonged period.

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POLYMERIC DIFFUSION MATRIX CONTAINING 5-[(3,4-DIMETHOXYPHENETHYL)METHYLAMINO]-2-(3,4-DIMETHOXYPHENYL)-2-ISOPROPYLVALERONITRILE

The present invention relates to a polymeric diffusion matrix containing 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile, also known as Verapamil. More particularly, the invention relates to a polymeric diffusion matrix containing 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile characterized by a sustained release of the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile. 5-[(3,4-Dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is a well known drug which acts as a calcium permeability blocking agent and is employed against angina pectoris and other heart disorders which respond to calcium permeability blocking.

A self-supporting polymeric diffusion matrix is provided for the sustained release of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile in order to deliver said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to a patient and provide said patient with an anti-angina effect, said matrix comprising from about 1 to about 60% by weight of a polar plasticizer; from about 6 to about 30% by weight polyvinylalcohol; form about 2 to about 30% by weight polyvinylpyrrolidone; and a pharmaceutically effective amount of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile about 2

to 5% by weight, to provide a sustained release of said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile over a prolonged period.

Polar plasticizers suitable for use in this invention include principally poly-lower alkylene oxides, but other polar plasticizers such as diethylphthalic diethylphthalate may be used.

In one embodiment the polar plasticizer is glycerol present in an amount of from about 2 to about 60% by weight. In another embodiment the polar plasticizer is polyethylene glycol present in an amount of from about 1 to about 15% by weight. A still further embodiment contemplates a mixture of glycerol and polyethylene glycol wherein the latter is present in an amount by weight of from about 1 to about 5 parts per weight glycerol.

The self-supporting polymeric diffusion matrix generally contains a mixture of polyvinylalcohol and polyvinylpyrrolidone, although it will be understood that other polymeric mixtures may be used provided they yield the desired sustained release effect. For example, both the polyvinylalcohol and the polyvinylpyrrolidone may be partially or completely replaced with from about 1 to about 9% agar or agarose, and preferably from about 1.5 to 3% agar or agarose, 2% agar or agarose being particularly preferred.

As the polyvinylalcohol used in the present invention, there is generally contemplated one having a molecular weight from about 50,000 to about 150,000, and more preferably about 100,000 to about 150,000, 115,000 having been used in related systems of the inventors with success. The polyvinylalcohol should be hydrolyzed, generally at least to the extent of 90% with a preferred embodiment being at least 95% hydrolyzed. The polyvinylpyrrolidone should have a molecular weight of

from about 15,000 to about 85,000, and more preferably from about 20,000 to about 60,000. Polyvinylpyrrolidone with a molecular weight of 40,000 is particularly preferred.

The amount by weight of the ingredients other than the polar plasticizer generally should be in the following ranges: Polyvinylalcohol is generally present in an amount of from about 6 to about 30% by weight, with 20% being a preferred embodiment; polyvinylpyrrolidone is present generally in an amount of from about 2 to about 30% by weight, with about 10% being preferred.

In particular embodiments of this invention the total amount of polyvinylalcohol and polyvinylpyrrolidone used is from about 25 to about 50% by weight.

The water-soluble polymer can be replaced with (in addition to agar) gum arabic, gum tragacanth, polyacrylic acid, polymethacrylic acid, polyvinyloxazolidone, polyvinylmorpholinone, and polyvinylpiperidone.

Polyalkylene glycols (poly-lower alkylene oxides) such as polyethylene glycol and polypropylene glycol may replace all or part of the glycerol.

In forming the matrix, excess water is not required. In accordance with a preferred aspect of the invention, about 5% by weight 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is included in the diffusion matrix. The resultant homogeneous mixture is poured into forms preferably made of glass or stainless steel. For transdermal application, a diffusion matrix with a thickness of about 1 to about 3 mm is in accordance with a preferred aspect of this invention. This diffusion matrix can be cut to obtain the desired surface area once it is suitably cured.

The following methods may be used for preparing the diffusion matrix of the invention.

In one method, the matrix is formed at atmospheric pressure. Water and polar plasticizer are first mixed together. A polar plasticizer such as glycerol or polyethylene glycerol is a necessary component in the matrix. A matrix formed without a polar plasticizer is not flexible and has poor diffusional contact with the skin, causing unreliable diffusion release. The polyvinylalcohol and polyvinylpyrrolidone are then added to the polar plasticizer water mixture at room temperature with agitation. The mixture is heated to a temperature within the range of from 90 to about 95°C at atmospheric pressure to extend the polymers. If desired, the mixture may be maintained at an elevated temperature for a period of time, based on polymer stability, prior to addition of the drug. Thus, the mixture is stable for a period of time and may be kept for such a period before being mixed with the drug to be delivered to the patient. Thereafter, the mixture is temperature-adjusted and the drug to be applied to the patient is then added to the mixture, with thorough agitation. Once a homogeneous mixture of the polymer solution and drug is obtained, the mixture is read to be cast to form in a drug-containing diffusion matrix. After casting, the mixture is cooled to a temperature such that gelation occurs.

In another method, the polymeric material is heated under pressure to accomplish dissolution in the mixture, the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is mixed in and the material is extruded under pressure into a mold of suitable size and geometry. The use of pressure allows for the incorporation of higher amounts of polymeric material into the matrix, up to 60% total polyvinylpyrrolidone and polyvinylalcohol content, thus improving film strength content, and dimensional stability and

allowing for thinner matrices. This pressure method further reduces or eliminates altogether curing and/or drying time.

It has been further found that curing is facilitated by subjecting the matrix to a temperature down to about -20°C immediately after casting, especially when polyethylene glycol is used as the plasticizer. The setting time is quickened considerably.

Sodium dodecyl sulfate or sorbitan (Tween-20) or other detergents may be added in an amount of 0.1 to 10% by weight, based on the matrix, as a dispersing agent, if desired. Soy phosphatides may be added as drug solubilizing agents in a concentration of 0.1-10% by weight. Up to 10% of one or more absorption facilitators to insure skin penetration such as dimethylsulfoxide, decylmethylsulfoxime, or other penetration enhancers may also be added. Suitable preservatives, such as sodium benzoate, may be also added where indicated.

The present drug delivery device comprises the drug-containing diffusion matrix which can be applied as a transdermal patch with means for fastening the matrix to the skin of a patient. Such means can take various forms, such as an occlusive backing layer forming a kind of "bandage" with the diffusion matrix being held against the skin of a patient being treated. A polyethylene or Mylar tape is contemplated as one form of occlusive layer in accordance with the invention. It can also take the form of an elastic band, such as a cloth band, a rubbery band or other material. Here, the diffusion matrix is placed directly on the skin and held in place over the arm or wrist of the patient. An intermediate adhesive layer between the diffusion matrix and the skin capable of permitting the transdermal application of the drug can also be used.

The invention is illustrated by the following non-limiting examples:

EXAMPLE I

Together there are mixed 20 gm glycerol and 55 ml water. This mixture is heated to 90°C; after reaching at least 70°C, there are slowly added 15 gm polyvinyl-alcohol (polyvinylalcohol 100% hydrolyzed, molecular weight 115,000) and 8 gm polyvinylpyrrolidone (m.w. 40,000). The mixture is stirred at 90°C until solution is effected, which may take about 10 minutes; it will be appreciated that with larger quantities, a considerably longer period of time may be needed. 98 ml of this solution is then mixed with 2 gm 5-[(3,4-dimethoxyphen-ethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropyl-valeronitrile, this mixture then being mechanically stirred until homogeneous. The homogeneous mixture is then poured into forms made of glass or stainless steel which serve as templates to produce a diffusion matrix having a thickness of about 0.2 to 2 mm. This diffusion matrix is then cut into square pieces of about 1 inch on each side, i.e., to provide a total surface of about 6.5 cm^2.

The diffusion matrix is applied to the skin of a patient in need of an anti-anginal effect, the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile being transdermally delivered. The diffusion matrix is ideally applied to the skin of the patient by means of a single-piece bandage having the diffusion matrix in the center under the occlusive layer, the bandage being provided to the patient with a peel-of cover much like a "band-aid".

EXAMPLE II

In place of the glycerol of Example I, there is substituted 10 gm polyethylene glycol having a molecular

weight of 1000 and 10 ml water. The resultant diffusion matrix is more rigid than the of Example I.

EXAMPLE III

In place of the polyvinylalcohol and polyvinylpyrrolidone of Example I, there are substituted 2 gm agarose and 21 ml water, yielding a diffusion matrix for the delivery of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile.

EXAMPLE IV

The following mixture, listed in parts by weight, is heated under pressure, about 3 atmospheres being suitable, to 110-130°C:

Polyvinylalcohol	20 parts	(115,000 m.w.)
Polyvinylpyrrolidone	15 parts	(40,000 m.w.)
Polyethylene glycol	5 parts	(4,000 m.w.)
Glycerol	3 parts	
Verapamil	5 parts	
Water	to 100 parts	

This mixture is first prepared by heating polyvinylalcohol and water to effect dissolution. The polyethylene glycol molecular weight 4000, polyvinylpyrrolidone and glycerol are dissolved in cold water, and the two aqueous mixtures are brought together under heat and pressure as described above. Finely divided 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is rapidly mixed into the viscous liquid and the mixture is extruded into an appropriate mold.

EXAMPLE V

In place of polyethylene glycol molecular weight 4000, of Example IV, polyethylene glycol molecular weight 1000 is used in the mixture.

WHAT IS CLAIMED IS

1. A self-supporting polymeric diffusion matrix for the sustained release of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile in order to deliver said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to a patient and provide said patient with an anti-anginal effect and relief from other heart disorders, said matrix comprising from about 1 to about 60% of a polar plasticizer, from about 6 to about 30% by weight polyvinylalcohol, from about 2 to about 30% by weight polyvinylpyrrolidone, and about 2 to 5% of the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to provide a sustained release of said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile over a prolonged period.

2. The polymeric diffusion matrix of claim 1, wherein the total content of polyvinylalcohol and polyvinylpyrrolidone is from about 25% to about 60% by weight, based on the weight of the matrix.

3. The polymeric diffusion matrix of claim 1 or 2, wherein said polar plasticizer is glycerol.

4. The polymeric diffusion matrix of claim 3, wherein said polyvinylalcohol has a molecular weight of about 50,000 to about 150,000.

5. The polymeric diffusion matrix of claim 3, wherein said polyvinylalcohol has a molecular weight of about 100,000 to about 150,000.

6. The polymeric diffusion matrix of claim 3, wherein said polyvinylpyrrolidone has a molecular weight of from about 15,000 to about 85,000.

7. The polymeric diffusion matrix of claim 3, wherein said polyvinylpyrrolidone has a molecular weight of from about 20,000 to about 60,000.

8. The polymeric diffusion matrix of claim 1 or 2, wherein said polar plasticizer is polyethylene glycol present in an amount of about 1 to about 15% weight.

9. The polymeric diffusion matrix of claim 1 or 2, wherein said polar plasticizer is a mixture of glycerol and polyethylene glycol, wherein said polyethylene glycol is present in an amount by weight of from about 1 to 5 parts per weight glycerol.

10. The polymeric diffusion matrix of claim 1, wherein comprising about 20% by weight polyvinylalcohol of molecular weight about 115,000, about 15% by weight of polyvinylpyrrolidone of molecular weight about 40,000, about 5% by weight polyethylene glycol of molecular weight about 4000 and about 3% by weight glycerol.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/00925

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] A61L 15/03
U.S. Cl. 424/28; 424/78; 424/80

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/28, 424/78, 424/80

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Chemical Abstracts

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
P	U.S., A, 4,291,015, Published 22 September 1981, KEITH et al	1 to 10
A	U.S., A, 4,210,633, Published 1 July 1980, TAKRURI et al	1 to 10
A	U.S., A, 3,742,951, Published 3 July 1973, ZAFFARONI	1 to 10
A	U.S., A, 3,287,222, Published 22 November 1966, LARDE et al	1 to 10
A	U.S., A, 2,693,438, Published 2 November 1954, WARD	1 to 10
A	U.S., A, 2,155,658, Published 25 April 1939, HORRMANN et al	1 to 10
A	U.S., A, 2,160,503, Published 30 May 1939, HORRMANN et al	1 to 10
A	GB, A, 493561, Published 11 October 1938, VOHRER	1 to 10

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
14 October 1982	19 OCT 1982
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Shep K. Rose

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	Chemical Abstracts Volume 94, Issued 1981 (Columbus, Ohio, USA) see page 311 column 2 the ABSTRACT 94: 20412e, KEITH et al (KEY PHARMACEUTICALS, INC.) EUR. PAT. APPL. 13,606, 23 July 1980, "POLYMERIC DIFFUSION MATRIX AND DRUG DELIVERY DEVICE COMPRISING SAID MATRIX"	1 to 10
A	Chemical Abstracts Volume 86, Issued 1977 (Columbus, Ohio, USA) see page 380 columns 1 and 2 ABSTRACT 86: 161344f SASUKI et al JAPAN KOKAI 76,112,511, 26 March 1975, "CATHPLASM"	1 to 10

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, 16 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No 18
A	Chemical Abstracts Volume 47, Issued 1953 (Columbus, Ohio, USA) see column 7165 DEF ITO et al BULL. PHARM. RESEARCH. INST. JAPAN. NO. 2: 1-12, "PHARMACEUTICAL STUDIES ON OINTMENTS AND EXTERNAL REMEDIES"	1 to 10
A	Chemical Abstracts Volume 92, Issued 1980 see page 350 column 2 ABSTRACT 92: 169275D, ANIKAWA et al JPN. KOKAI TOKKYO KOHO 79,151,115, 28 November 1979, "MEDICATED WET PACKS" (Columbus Ohio USA)	1 to 10
A	Chemical Abstracts Volume 89, Issued 1978 (Columbus Ohio USA) see page 548 column 1 ABSTRACT 89: 117911b, ARAI et al JAPAN KOKAI 78 50,320, 08 May 1978, "HYDROPHILIC PLASTERS"	1 to 10
A	Chemical Abstracts Volume 87, Issued 1977 (Columbus, Ohio, USA) see page 330 column 1 ABSTRACT 87: 141303j, TAURA et al, JAPAN KOKAI 77 38016, 24 March 1977, "POULTICES"	1 to 10